Review Article

Beyond Insulin: How CRISPR-Cas9 is Reshaping the Future of Diabetes Treatment

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ABSTRACT

Diabetes mellitus remains one of the most pressing global health challenges, with existing treatments focused primarily on managing symptoms rather than addressing root causes. CRISPR-Cas9 genome editing technology offers an opportunity to reshape therapeutic strategies for type 1 and type 2 diabetes. In type 1 diabetes, CRISPR is utilized to enhance the survival and function of insulin-producing cells and mitigate harmful immune responses. For type 2 diabetes, researchers focus on how genetic interventions can help regulate blood sugar levels and reduce inflammation. This review highlights current clinical applications and various ethical considerations related to germline editing, equitable access, and off-target risks. Through the explanation of cutting-edge research, this review highlights the role of CRISPR-Cas9 in shaping the future of diabetes therapy.

Keywords: Diabetes Mellitus; CRISPR technology; Genome Editing; Type 1 Diabetes; Type 2 Diabetes; Beta Cell Regeneration; Gene Therapy; Ethical Considerations

INTRODUCTION

Diabetes mellitus (known as diabetes) is one of the most widespread chronic diseases globally, currently affecting 830 million individuals (1). Characterized as a metabolic disease that results in elevated blood glucose levels, diabetes profoundly impacts an individual's daily life, disrupting bodily functions and limiting dietary choices. The two most prevalent types of this disease are known as type 1 and type 2 diabetes. Type 1 diabetes is an autoimmune, genetically inherited condition in which the pancreas produces little to no insulin. In contrast, type 2 diabetes is a progressive disorder characterized by insulin resistance and impaired insulin production. Despite the availability of various therapeutic strategies, such as insulin therapy and lifestyle interventions, current treatments focus on managing the disease rather than offering a definitive cure.

In response to the growing burden of diabetes, advances in genomic science have paved the way for new, innovative treatment approaches, ushering in improved possibilities of an enhanced lifestyle for diabetic patients. Discovered originally as part of bacterial defenses against phages and plasmids, CRISPR (Clustered Regularly Interspaced Short Palindromic Repeats) has been repurposed as a powerful genome-editing tool for various organisms and cell types, with applications ranging from

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cancer treatment to the treatment of genetic disorders (2). Now, CRISPR-Cas9 is emerging as a promising option in the treatment of diabetes.

The convergence of diabetes research and CRISPR-Cas9 technology presents a significant opportunity for elucidating the genetics of the disease, its progression, and potential therapies. For instance, CRISPR-Cas9 systems combat type 1 diabetes through stem cell therapy, epigenetic editing, and the activation of endogenous insulin, all without altering the DNA. In type 2 diabetes, CRISPR-Cas9 offers excellent insights into insulin signaling and gene regulation (3). However, as these applications develop, they raise critical questions regarding safety, ethical issues, delivery mechanisms, and clinical utilization.

This paper explores the intersection of diabetes and CRISPR-Cas9 technology by examining the biological foundations of both fields, evaluating current research on various therapeutic applications, and discussing the prospects and ethical implications of genome editing using CRISPR-Cas9 in diabetes treatment.

UNDERSTANDING DIABETES

Types and Pathophysiology

Diabetes mellitus includes a vast group of metabolic disorders characterized by chronic hyperglycemia resulting from defects in insulin action, insulin secretion, or both. It is a varied disease with various underlying mechanisms that differ across its distinct forms. The primary types of diabetes include type 1 diabetes (T1D) and type 2 diabetes (T2D) (4). Understanding the pathophysiology behind each form of diabetes mellitus is essential for developing effective prevention and treatment strategies.

Type 1 Diabetes Mellitus (T1D)

T1D accounts for approximately 5-10% of all diabetes cases in the United States and typically begins in childhood or adolescence, although it can occur at any age (5). It is an autoimmune disorder characterized by the destruction of pancreatic beta cells, leading to a scarcity of insulin production (4, 5). The autoimmune attack involves T lymphocytes that target pancreatic islet cells, accompanied by the presence of autoantibodies, such as those against glutamic acid decarboxylase (GAD), insulin, and islet antigen-2 (6, 7).

Genetic susceptibility plays a substantial role in T1D, with the strongest contributors on chromosome 6p21, particularly HLA class II alleles such as HLA-DR3 and HLA-DR4 (12). Variants HLA-DR3-DQ2 and HLA-DR4-DQ8, found in ~90% of affected children, increase the risk by enhancing the presentation of self-antigens to autoreactive T cells. In addition to HLA, over 15 loci, including LYP, PTPN22, and CTLA-4, further modulate susceptibility by impairing T-cell signaling and promoting beta-cell apoptosis (12). Epigenetic mechanisms, such as DNA methylation and histone modification, also contribute; hyperglycemia exposure can induce heritable epigenetic changes that predispose offspring to metabolic dysfunction (5).

The immune-mediated destruction of beta cells in T1D is a chronic progression. The preclinical phase involves the development of islet autoantibodies, followed by a phase of dysglycemia as insulin production decreases. Ultimately, an excessive loss of beta cell mass occurs, resulting in hyperglycemia. CD8+ cytotoxic T cells are mainly responsible for beta cell destruction, aided by CD4+ helper T cells, macrophages, and dendritic cells. These immune cells enter the islets and trigger inflammation. This series of events leads to the loss of self-tolerance of autoantigens and initiates autoimmunity, leading to T1D (Figure 1) (6, 7).

Type 2 Diabetes Mellitus (T2D)

T2D is the most common form of diabetes, with 90-95% of cases in the United States encompassing this form. It is a metabolic disorder characterized by a combination of insulin resistance and progressive beta cell dysfunction, leading to severe insulin deficiency (4, 5). While this type most commonly affects adults, the incidence in children and adolescents has risen dramatically due to increasing obesity rates in the United States, with a 25-45% increase in the number of youth diagnosed with T2D diabetes (8).

Compared to T1D, T2D does not involve the autoimmune destruction of beta cells. Instead, genetic predisposition, obesity, physical inactivity, and dietary habits contribute to insulin resistance (5). In T2D, insulin sensitivity, known as how well one's body responds to insulin, decreases. This mechanism allows the pancreas to compensate for this issue by increasing insulin secretion. Eventually, this response fails, and hyperglycemia develops. In addition to insulin resistance, individuals with T2D may exhibit increased hepatic glucose output, impaired incretin effects, and altered lipid metabolism. Adipose tissue dysfunction in T2D contributes to chronic, low-grade inflammation, impacting insulin signaling (9).

T2D pathophysiology involves a complex progression characterized by insulin resistance and beta cell dysfunction. Initially, insulin resistance in skeletal

muscle, liver, kidneys, small intestine, brain, and adipose tissue induces hyperglycemia, as beta cells compensate for this loss of insulin by secreting greater amounts of insulin. However, prolonged metabolic stress leads to exhausted beta cell systems, apoptosis, and inadequate insulin production (Figure 2) (9).

Key mechanisms include (9):

- Adipose Tissue Inflammation: An endocrine organ that releases adipokines, cytokines, and chemokines, in which an increase in this tissue inflammation directly correlates to T2D (10).
- Lipotoxicity and Glucotoxicity: Chronic exposure to elevated fatty acids and glucose induces oxidative and ER stress in beta cells, resulting in apoptosis.
- Mitochondrial dysfunction: Impaired mitochondrial function in beta cells increases oxidative damage and reduces ATP production, which is crucial for insulin secretion.
- Hepatic Insulin resistance: The liver produces glucose despite elevated insulin levels, producing hyperglycemia.

Beyond these pathophysiological mechanisms, T2D is strongly influenced by polygenic susceptibility. Genome-wide association studies (GWAS) have identified over 400 loci associated with glycemic traits, insulin secretion, and insulin resistance. Notable genes include TCF7L2, which affects insulin secretion, and FTO, which is associated with obesity and an increased risk of T2D (11, 14). Collectively, these variants in the loci influence pancreatic beta cell function, hepatic glucose production, and insulin action in peripheral tissues. Despite the polygenic nature

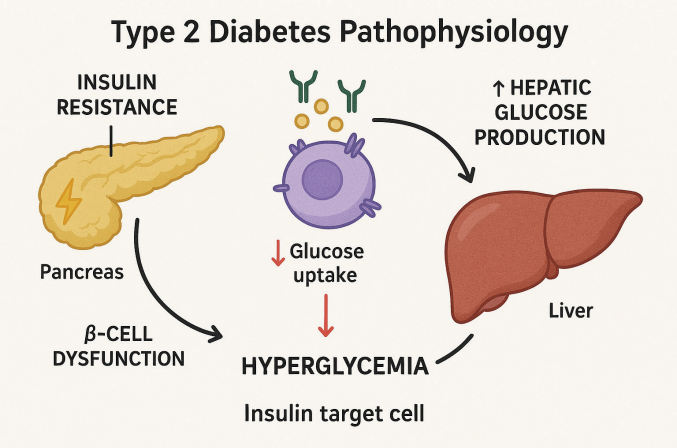

Figure 2. Pathophysiology of T2D. This diagram illustrates the core mechanisms of T2D pathophysiology, emphasizing how insulin resistance, β-cell dysfunction, and increased hepatic glucose production collectively lead to chronic hyperglycemia. It highlights the impaired glucose uptake in peripheral tissues and the liver's role in exacerbating blood glucose levels.

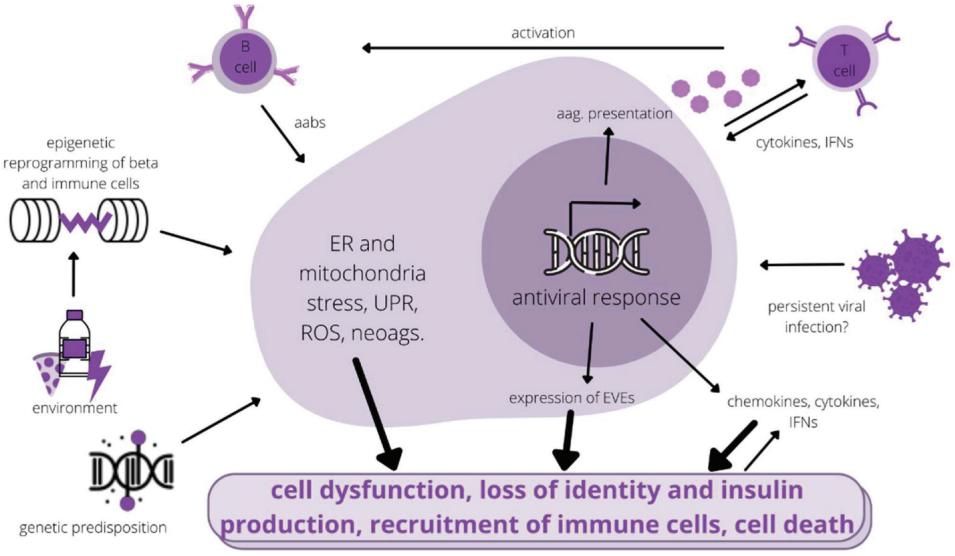

Figure 1. Pathophysiology of T1D (14). Adapted from: [Zajec, *et al*., 2022], with permission from [MDPI]. This diagram illustrates how genetic predisposition and viral infections contribute to beta-cell stress and immune activation in T1D. These factors ultimately lead to beta cell dysfunction, loss of insulin production, and cell death through complex immune and antiviral responses, which collectively enable the development of T1D.

of T2D, heritability estimates of T2D range from 26% to 80%, depending on the ethnicity and environmental context (14). Taken together, the genetic and metabolic distinctions between T1D and T2D are summarized in Table 1.

While diabetes remains challenging to manage due to its complex genetic and metabolic drivers, emerging genome-editing tools, such as CRISPR-Cas9, offer a novel path forward by directly targeting these underlying mechanisms.

UNDERSTANDING THE CRISPR-CAS9 SYSTEM

Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR) and CRISPR-associated (Cas) proteins have revolutionized genetic engineering. Initially discovered in prokaryotic immune systems, CRISPR-Cas9 has been adapted as a tool for genome editing with great precision and efficiency. Its development has enabled researchers to manipulate the genetic code in innovative ways, with applications spanning medicine, agriculture, and biotechnology.

CRISPR was first observed in 1987 as repeated sequences in the DNA of *Escherichia coli*. These sequences, interspaced with unique vital fragments, were later recognized as an immune feature of bacteria and archaea (15). Evolved from earlier gene editing tools such as zinc finger nucleases (ZFNs) or transcription activator-like effector nucleases (TALENs), which require a custom-designed protein for each target, CRISPR-Cas9 requires only a change in the 20-nucleotide guide RNA sequence to target a new locus. In prokaryotes, CRISPR functions as a genetic memory system. When bacteria are invaded by foreign elements, such as bacteriophages or plasmids, they integrate segments of the invader's DNA into their genome as "spacers." These sequences are transcribed into CRISPR RNAs (crRNAs), guiding Cas proteins to recognize and destroy future invasions using the same DNA sequence (2).

Three primary components of CRISPR help the CRISPR-Cas9 system function (15, 16):

- **Cas9 protein:** A DNA endonuclease enzyme that introduces double-stranded breaks at specific genomic locations.
- **Guide RNA (gRNA):** A synthetic RNA molecule that combines features of crRNA and trans-activating crRNA (tracrRNA), known as single guide RNA (sgRNA)
- **Protospacer Adjacent Motif (PAM):** A short sequence in the target DNA, crucial for Cas9 activity

These components form a system that enables the recognition and cleavage of a specific site of DNA.

Cas9 begins searching for target DNA by scanning the genome for PAM sequences. Without PAM, Cas9 cannot bind the DNA, even if the sequence perfectly matches the guide RNA. The PAM is an essential safety feature that prevents the bacterial immune system from targeting its genome (15).

Once PAM is located, the Cas9-sgRNA complex unwinds the adjacent DNA sequence. If the 20-nucleotide region of the guide RNA is complementary to the DNA, it forms an RNA-DNA hybrid through Watson-Crick base pairing. This process is facilitated by conformational changes in Cas9 that position its nuclease domains for

Table 1. Overview of the Different Types of Diabetes Mellitus

Feature	T1D	T2D
Age of Onset	Childhood/Adolescence	Adulthood (increasing in youth)
Insulin Deficiency	Absolute	Relative
Beta Cell Involvement	Autoimmune destruction	Functional Decline
Insulin Resistance	Minimal	Prominent
Genetic Influence	Strong (HLA-linked)	Strong (polygenic)
Autoimmunity	Present	Absent
Reversibility	No	Potentially with intervention

This table provides a side-by-side comparison of type 1 and type 2 diabetes, highlighting their key difference in onset, underlying mechanisms, genetic influence, and potential for reversibility.

cleavage (15, 16).

The Cas9 protein contains two nuclease domains. The HNH domain within the Cas9 protein cleaves the DNA strand complementary to the guide RNA. The RuvC domain, also within the Cas9 domain, cuts the non-complementary strand (16). The result of these steps is a blunt-ended double-stranded break at a specific genome site. For Cas9 to bind and cleave, the DNA target must be adjacent to PAM (Figure 3).

After cleavage, the cell's DNA repair takes over, with two possible pathways:

Non-Homologous End Joining (NHEJ): A rapid, error-prone mechanism that can introduce insertions or deletions at the break site, commonly used for gene disruption (16).

Homology-directed Repair (HDR): A precise mechanism that uses a homologous DNA template to insert correct genetic sequences. This pathway enables specific edits when a repair template is provided (2, 17).

For diabetes therapy, NHEJ is more suitable for gene knockouts such as RNLS. At the same time, HDR is preferable in precise gene correction applications, such as SLC30A8 editing, with its low efficiency in human cells being a considerable barrier.

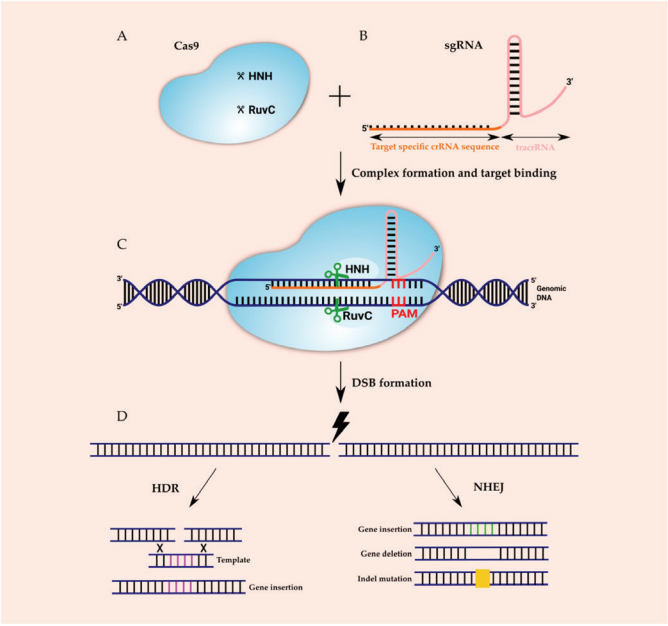

Figure 3. Mechanism of CRISPR-Cas9 Genome Editing (40). Adapted from: [Janik, *et al*., 2020], with permission from [MDPI]. This diagram outlines the molecular process of CRISPR-Cas9 functions. It details how the Cas9 protein, guided by sgRNA, locates and binds to the target DNA sequence adjacent to a PAM sequence. Upon correct binding, Cas9 introduces a double-stranded break at the desired genomic site, allowing for subsequent gene editing through the NHEJ or HDR pathways.

In summary, the CRISPR-Cas9 system provides a highly adaptable and efficient method for targeted genome editing, with NHEJ and HDR offering distinct avenues for gene disruption and precise correction. While delivery and repair efficiency remain challenges, the system's programmability makes it a powerful platform for therapeutic innovation. Building on this foundation, researchers are now applying CRISPR to diabetes, targeting genes that regulate immune function, beta cell survival, and metabolic pathways.

CRISPR IN DIABETES - FROM RESEARCH TO THERAPEUTIC APPLICATIONS

Gene Targets in Type 1 & 2 Diabetes

The genetics behind diabetes mellitus is detailed and intricate, involving numerous loci that contribute to the development and progression of both T1D and T2D. The development of CRISPR-based genomics has enabled researchers to target specific genes with great precision. This section utilizes findings from studies that use CRISPR-Cas9 in detail to identify and validate key genes and networks in diabetes pathogenesis (Table 2).

Pleiotropic Gene loci & Cross-Type Insights

T1D and T2D have been considered genetically distinct. However, recent evidence has demonstrated that several loci are pleiotropic, which confer susceptibility to both forms of the disease. Chromatin interaction mapping (Hi-C) and spatial expression quantitative trait locus (eQTL) integration to identify 195 pleiotropic genes influenced by tissue-specific regulatory elements. Genes such as TCF7L2, RREB1, and GLIS3 were functionally linked to autoimmune and metabolic pathways (18). The loci showed enrichment for pathways involving insulin signaling, cytokine regulation, and mitochondrial function, sharing a genetic basis that could unify understanding across diabetes subtypes and unified therapeutic targets (19).

T1D Gene Targets

The primary genetic contributors to T1D include the HLA class II region, INS, PTPN22, and IL2RA. These genes regulate immune tolerance, T-cell activation, and beta-cell antigen presentation (20). Multiple non-HLA loci, including those involved in cytokine signaling and beta cell stress responses, were highlighted as key mediators of early T1D risk.

Table 2. Overview of CRISPR-Associated Genes and Mechanisms Applied in Diabetes Mellitus

Diabetes Type	Target/Approach	Gene(s) Involved	Mechanism/Outcome
T1D	Increase beta cell resilience	RNLS	Knockout of RNLS reduced oxidative/ER stress and CD8+ T cell-mediated apoptosis, improving beta cell survival
	Immune evasion of beta cells	B2M (knockout), PD-L1 (insertion)	Prevents immune recognition by removing MHC-I component and adding an immune checkpoint molecule; supports islet transplantation without immunosuppressants
	INS gene activation	INS (CRISPRa, not editing)	Reactivated insulin production in fibroblasts using CRISPR fused to activation domains, avoiding DNA sequence changes
	Gene correction in patient-derived cells	PTPN22, UBASH3A	Corrects autoimmune-related gene variants; improves beta-like cell function and reduces immune system reactivation
T2D	Enhance insulin secretion	DPP4	Disruption of DPP4 increases GLP-1 levels, improving insulin secretion and reducing blood glucose in mice
	Reduce inflammation and insulin resistance	NLRP3	Inhibiting NLRP3 reduced inflammasome-related beta cell damage and improved insulin sensitivity
	Improve blood flow and reduce fibrosis	RXFP1 (overexpression)	CRISPR-modified adipose-derived stem cells overexpress RXFP1, enhancing tissue repair in diabetic models

This table categorizes key gene targets and CRISPR-mediated approaches for T1D and T2D. It outlines gene-specific strategies such as RNLS knockout to improve beta cell survival, B2M/PD-L1 editing for immune evasion, and DPP4 or NLRP3 modification to enhance insulin secretion and reduce inflammation.

The IL2RA gene encodes the alpha subunit (CD25) of the interleukin-2 receptor complex, which is essential for the development and function of regulatory T cells — cells that suppress autoimmune responses. Genetic variants in IL2RA are strongly associated with an increased risk of T1D. Those with IL2RA polymorphisms carrying T1D-associated risk alleles had reduced interleukin-2 signaling, as shown by lower phosphorylation levels of the downstream signal transducer STAT5a in CD4+ T cells (21). This signaling defect impaired the expression of FOXP3, the transcription factor that maintains T cells' identity and function.

T cells from individuals with IL2RA risk variants exhibited compromised suppressive ability, indicating that they were less capable of inhibiting the proliferation of autoreactive T cells. This breakdown in immune regulation creates an environment that facilitates the autoimmune destruction of beta cells, thereby contributing directly to the pathogenesis of diabetes through immune dysfunction (21).

Regulatory elements such as enhancers also play a crucial role in T1D. A distant enhancer region controls the expression of ONECUT1, a transcription factor essential for pancreatic development and B-cell maturation. Using CRISPRi, a specific study successfully silenced the enhancer and observed the regulation of pancreatic differentiation markers, suggesting that T1D may involve dysregulation of both immune pathways (22).

T2D Gene Targets

The TCF7L2 (Transcription Factor 7-Like 2) gene is the strongest and most associated with T2D. This gene is crucial in the Wnt signaling pathway, which regulates beta cell proliferation, glucose metabolism, and insulin secretion (23). Regulatory variants at the TCF7L2 locus influence a broad network of interacting genes. A study utilizing chromatin conformation analyses reveals that enhancers come into contact with distant promoters,

involved in both beta cell function and inflammatory pathways, suggesting that TCF7L2 acts as a transcription factor and regulates and coordinates gene networks in diabetes (18). TCF7L2 variants have been associated with reduced insulin secretion and altered incretin response, progressing diabetes, and affecting its treatment.

PDX1 (Pancreatic and Duodenal Homeobox 1) is a transcription factor essential for pancreatic development and the function of adult beta cells. Reduced PDX1 expression is associated with impaired insulin gene transcription and beta cell dysfunction in diabetes (24).

SLC30A8: This gene encodes ZnT8, a zinc transporter that localizes to insulin granules. Zinc is needed for insulin storage and regulated secretion (25). CRISPR-Cas9 was used to knock down SLC30A8 in beta cell models, leading to altered insulin secretion and deficient insulin production.

GLIS3 (GLIS Family Zinc Finger 3) functions in beta cell development and insulin gene regulation. It also controls resistance to cellular stress, including oxidative and ER stress, prominent in T2D pathology (26).

Among these, TCF7L2 emerges as the most promising therapeutic target due to its influence on both beta cell function and inflammatory pathways. It offers potential for broader metabolic reprogramming compared to single-function genes, such as SLC30A8.

CRISPR-Driven Therapeutic Strategies in Diabetes

Diabetes is a globally prevalent disorder characterized by chronic hyperglycemia resulting from defects in insulin secretion and/or insulin action. CRISPR-Cas9 genome editing is a revolutionary tool that offers current therapeutic strategies leveraging CRISPR in T1D and T2D, incorporating approaches ranging from cell reprogramming to gene correction.

Therapeutic Applications in T1D

In T1D, autoimmune destruction of the pancreatic beta cells results in insulin deficiency (4, 5). The CRISPR-Cas9 system offers a direct method to increase beta cell resilience and reduce immune-mediated attack. A study utilized CRISPR to knock out the RNLS gene, essential in modulating oxidative and ER stress in beta cells. Deletion of RNLS significantly improves beta cell survival under autoimmune conditions, reducing their vulnerability to CD8+ T cell-mediated apoptosis and the prevalence of T1D. Further strategies include making beta cells "invisible" to the immune system. Editing out B2-microglobulin (B2M), a core component of MHC-I, a molecule that aids in the development of T1D, and then inserting PD-L1, an immune checkpoint molecule, renders these cells resistant to immune recognition. These cells can be used for islet transplantation without the need for drugs (3).

T1D patient-derived fibroblasts, cells that play a crucial role in both wound healing and fibrosis, have been treated with CRISPR-Cas9 fused to activation domains to regulate the INS gene expression without changing the DNA sequence, enabling a reactivation of insulin production pathways, resulting in an overall non-invasive alternative to DNA-editing-based approaches to combat T1D (3, 27).

CRISPR has been applied to correct T1D-associated variants in patients. T1D-associated variants can then be differentiated into beta-like cells for potential transplantation. For instance, variants in PTPN22 and UBASH3A, known as autoimmune-related genes, have been identified as reducing autoreactivity and improving beta cell compatibility (28).

Therapeutic Applications in T2D

CRISPR has been deployed to regulate metabolic genes involved in glucose handling. One primary target is the DPP4 gene, which encodes dipeptidyl peptidase, an enzyme responsible for degrading glucagon-like peptide-1 (GLP-1), a key incretin hormone that stimulates insulin secretion in response to food intake. Using diabetic mouse models, CRISPR-mediated DPP4 knockout resulted in a sustained elevation of GLP-1 levels, significantly reducing blood glucose levels and improving liver and kidney function, suggesting both glycemic and systemic metabolic benefits (3). The NLRP3 inflammasome, a multiprotein complex that senses cellular stress and activates pro-inflammatory cytokines, has also emerged as a promising therapeutic target. CRISPR-mediated inhibition of NLRP3 in immune cells alleviated inflammation-induced beta cell dysfunction and improved insulin sensitivity in obese mouse models (29). This approach is particularly relevant to T2D, where chronic inflammation plays a central role in disease progression. In addition, adipose-derived stem cell (ADSC) engineering using CRISPR to overexpress receptors in diabetic tissues has been shown to reduce fibrosis. These effects translate into improved wound healing and tissue regeneration, which can be extremely useful for regenerative medicinal applications in diabetes (3). Compared to pharmacologic interventions that act downstream, these gene-editing strategies can offer a potentially longer-lasting and more targeted approach to managing insulin resistance, inflammation, and tissue degeneration in diabetes.

Clinical Trials with CRISPR-Cas9 and Diabetes

CRISPR-Cas9 technology and its potential applications in treating diabetes have garnered significant attention. However, transitioning CRISPR-based therapies from research to clinical practice involved navigating various clinical trials.

VCTX210: Gene-edited Pancreatic Cell Therapy

A significant milestone in the clinical application of CRISPR and diabetes is the VCTX210 program. This therapy, developed in collaboration between CRISPR Therapeutics and ViaCyte, is an allogeneic, gene-edited, stem cell-derived pancreatic cell product designed for individuals with T1D. Using CRISPR-Cas9, the cells are engineered to secrete insulin and evade immune detection by knocking out the B2M gene and inserting Pd-L1, thereby reducing recognition by cytotoxic T cells and minimizing immune rejection (3). Encapsulated and then transplanted into the patient, these cells are intended to function as a long-term insulin source without requiring immunosuppressive therapy, which has been a key limitation in earlier therapies, such as Lantidra, that require long-term immunosuppression (30). As of 2024, VCTX210 remains in Phase 1 clinical trials to assess its safety, tolerability, and potential for insulin production (31). However, its use of immune cloaking mechanisms and design holds great promise for reshaped beta cell replacement strategies in autoimmune diabetes.

CRISPR Programming of Adipose Tissue

CRISPR has been used to target metabolic pathways in adipose tissue. Researchers applied CRISPR technology to convert white adipose cells into brown-like fat cells, thereby promoting thermogenesis and enhancing insulin sensitivity. This option addresses T2D and obesity by altering fat cell rate and enhancing energy expenditure, offering an alternative to classical beta cell replacement strategies (32).

Ethical Considerations of CRISPR-Cas9 and Diabetes

One of the most debated ethical issues in CRISPR is germline gene editing, which involves altering genetic material in eggs, sperm, or embryos that would be passed on to future generations (33, 41). While multiple genes and environmental triggers influence T1D, germline modifications could theoretically target risk alleles such as HLA variants or IL2RA. However, the inheritable and permanent nature of these edits raises unresolved concerns about long-term safety and a lack of consent from future generations. In 2021, the World Health Organization (WHO) released a governance framework that called for a ban on heritable genome editing and promoted transparency, equity, and accountability (34, 35). Somatic editing, restricted to non-reproductive cells, is considered more ethically permissible for severe conditions like T1D, although risks of immune reactions and off-target mutations remain. Countries differ widely: China and Russia have moved ahead with early germline interventions, while Canada and the European Union enforce stricter prohibitions (36).

As CRISPR therapies advance into clinical use for diabetes, informed consent becomes essential. Participants in the early-stage trials must clearly understand not only the potential benefits but also the experimental nature of these treatments and their uncertainties, including off-target effects, immune response, and incomplete gene edits. Ensuring that consent processes prioritize patient autonomy is crucial for aligning with both ethical and legal standards (37).

Off-target editing is another major issue in genome editing, which can disrupt normal cellular behavior, trigger immune dysfunction, or cause tumorigenesis (38). For diabetes applications, these unintended effects represent serious safety risks that demand strict oversight. Ethical justification requires comprehensive safeguards, including preclinical modeling and long-term follow-up, to minimize harm and maintain research integrity (39).

Ultimately, questions of access and governance are crucial to the ethical use of CRISPR. Advanced gene therapies are costly and resource-intensive, raising the possibility of deepening health inequities, particularly since diabetes disproportionately affects low-income and marginalized groups (40). Ethical integration of CRISPR requires affordability, inclusion in public health systems, and oversight through review boards, public engagement, and international coalitions. Without such measures, decentralized, market-driven development could erode public trust and compromise safety (41). Ensuring collaboration among scientists, regulators, ethicists, and patient communities will be vital to striking a balance between innovation and responsibility as CRISPR-Cas9 becomes a tool for managing and potentially curing diabetes.

FUTURE PROSPECTS

The future of CRISPR-Cas9 in diabetes therapy lies in translating experimental successes into durable, clinically relevant applications. In T1D, strategies such as

immune-evasive beta cells (B2M knockout with Pd-L1) insertion and RNLS knockout for stress resistance offer a pathway toward transplantation therapies without lifelong immunosuppression. Stem-cell-derived islets engineering with CRISPR may provide scalable "off-the-shelf" treatments, especially when combined with encapsulation technologies. For T2D, CRISPR interventions targeting metabolic genes, such as DPP4 and NLRP3, show promise in restoring insulin sensitivity, reducing inflammation, and improving systemic metabolism. Expanding CRISPR to reprogram adipose tissue or enhance tissue regeneration introduces novel therapeutic avenues beyond glycemic control.

Advancements in base editing and prime editing may overcome current efficiency and safety barriers by avoiding double-strand breaks and enabling precise single-nucleotide corrections. Integrating CRISPR screens with GWAS and epigenetic editing could accelerate the discovery of regulatory elements, enhancers, and non-coding RNAs critical to diabetes susceptibility. However, widespread implementation will require progress in delivery systems, particularly in the development of non-viral vectors and tissue-specific targeting. Ethical governance, ensuring equitable access, informed consent, and long-term monitoring, will remain central as CRISPR therapies progress towards mainstream use.

CONCLUSION

CRISPR-Cas9 represents a transformative shift in diabetes research, moving beyond symptom management toward disease modification and potential reversal. By enabling precise edits in genes regulating immune tolerance, beta cell survival, and metabolic pathways, CRISPR provides tools to address both autoimmune and metabolic drivers of diabetes. Clinical initiatives such as VCTX210 highlight the feasibility of gene-edited, immune-shielded pancreatic cells. At the same time, preclinical studies underscore the potential of CRISPR in modulating inflammation, enhancing insulin secretion, and repairing tissue damage.

Despite the challenges of off-target effects, delivery inefficiencies, and ethical considerations, ongoing innovation in editing tools, such as base and prime editors, strengthens the case for CRISPR as a cornerstone of future therapies. If coupled with responsible governance and equitable access, CRISPR-based interventions may redefine diabetes treatment, offering not just control but durable remission or prevention for millions worldwide.

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